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Non-cardiac comorbidities in heart failure with reduced, mid-range and preserved ejection fraction☆

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ABSTRACT

Background: Comorbidities play a major role in heart failure. Whether prevalence and prognostic importance of comorbidities differ between heart failure with preserved ejection fraction (HFpEF), mid-range (HFmrEF) or reduced ejection fraction (HFrEF) is unknown.

Methods: Patients from index (n = 2516) and validation cohort (n = 1738) of The BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF) were pooled. Eight non-cardiac comorbidities were assessed; diabetes mellitus, thyroid dysfunction, obesity, anaemia, chronic kidney disease (CKD, estimated glomerular filtration rate < 60 mL/min/1.73 m^2), COPD, stroke and peripheral arterial disease. Patients were classified based on ejection fraction. The association of each comorbidity with quality of life (QoL), all-cause mortality and hospitalisation was evaluated.

Results: Patients with complete comorbidity data were included (n = 3499). Most prevalent comorbidity was CKD (50%). All comorbidities showed the highest prevalence in HFpEF, except for stroke. Prevalences of HFmrEF were in between the other entities. COPD was the comorbidity associated with the greatest reduction in QoL. In HFrEF, almost all were associated with a significant reduction in QoL, while in HFpEF only CKD and obesity were associated with a reduction. Most comorbidities in HFrEF were associated with an increased mortality risk, while in HFpEF only CKD, anaemia and COPD were associated with higher mortality risks.

Conclusions: The highest prevalence of comorbidities was seen in patients with HFpEF. Overall, comorbidities were associated with a lower QoL, but this was more pronounced in patients with HFrEF. Most comorbidities were associated with higher mortality risks, although the associations with diabetes were only present in patients with HFrEF.

1. Introduction

Heart failure (HF) is often accompanied by one or multiple non-cardiac comorbidities, making diagnosis and management of HF more complicated. These comorbidities are often associated with worse outcomes and higher hospitalisation rates [1–3]. It is known that HF and comorbidities such as chronic kidney disease (CKD, defined as glomerular

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filtration rate (GFR) < 60 mL/min/1.73 m^2), chronic obstructive pulmonary disease (COPD), diabetes mellitus, stroke and anaemia are often present in HF, and that CKD is associated with an increased mortality risk [4,5]. Studies have shown that comorbidities are more prevalent, are associated with a higher mortality risk and with more physical impairment in patients with heart failure with preserved ejection fraction (HFpEF) compared with patients with a reduced ejection fraction (HFrEF) [6–8]. However, the association of each of the separate comorbidities with mortality in patients with HF is currently unknown. Secondly, little is known about the association of individual non-cardiac comorbidities with quality of life (QoL) in patients with HFrEF, HFpEF and heart failure with mid-range ejection fraction (HFmrEF).

This study therefore aimed to investigate the associations between individual non-cardiac comorbidities and QoL and their association with mortality in patients with HFrEF, HFmrEF and HFpEF.

2. Methods

2.1. Study population

For the current study population, we have combined both the index cohort (n = 2516) and validation cohort (n = 1738) of the BIOSTAT-CHF (A systems BIOlogy Study to Tailored Treatment in Chronic Heart Failure), a multicentre, prospective observational study [9]. In the index cohort, primary inclusion criteria were an objective cardiac dysfunction, defined by either a left ventricular ejection fraction (LVEF) <40% or plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) of >2000 pg/mL and be treated with at least 40 mg of furosemide or equivalent, and were on sub-optimal dose of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers. Main inclusion criteria in the validation cohort were documented HF and patients had to be treated with at least 20 mg furosemide or equivalent per day and were anticipated to be up titrated with ACE inhibitors/ARBs and/or beta-blockers. Institutional review board approved the study, and all patients gave written informed consent. A full list of inclusion and exclusion criteria has been previously published [9]. Patients were divided based on LVEF into HFrEF (LVEF<40%), HFmrEF (LVEF 40–50%) and HFpEF (LVEF ≥50%) according to the most recent ESC HF guidelines [10]. Patients who had full data available for the 8 non-cardiac comorbidities stated below and who had available LVEF were included (n = 3499).

2.2. Non-cardiac comorbidities

Eight non-cardiac comorbidities were included in this analysis. Comorbidities included were diabetes mellitus (type I and type II diabetes), obesity (defined as a body mass index above or equal to 30 kg/m^2), thyroid dysfunction (both hypo- and hyperthyroid disease), chronic kidney disease (CKD) (defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2) measured at baseline, a history of stroke, chronic obstructive pulmonary disease (COPD), peripheral arterial disease (PAD) and anaemia (defined as a haemoglobin below 12 g/dL in woman and below 13 g/dL in men, measured at baseline) [11]. The presence of COPD, stroke, thyroid dysfunction, PAD or diabetes was assessed by the treating physicians, based on information available on the patients' medical history and during inclusion of the study.

2.3. Statistical analysis

Normally distributed data are presented as means and standard deviation, not normally distributed data as medians and 25th until 75th percentile, and categorical variables as percentages and frequencies. Intergroup differences between variables were tested using one-way ANOVA for normal distributed data; skewed data was tested using Chi-squared test or Kruskal-Wallis test depending on whether the data was continuous or nominal. Post-hoc analysis was performed to calculate differences between the groups. Prevalence of each of the comorbidities was also standardized for age. Age groups were created per 10 years, starting at 20 years up to 100 years. Per age group, the age specific prevalence in each of the HF subgroups was assessed, and multiplied by the total number of patients in that age category. This was done for each of the age groups, after which the sum of all the age groups was divided by the total number of patients. QoL was assessed by using the Kansas City Cardiomyopathy Questionnaire (KCCQ) and EuroQol five dimensions questionnaire (EQ-5D) [12,13]. A difference of ≥5 points between mean scores was considered to be minimally clinically important [13,14]. To evaluate the association of the comorbidities with KCCQ overall score, univariable and multivariable linear regression analysis was performed. Cox proportional hazard analysis was performed to analyze the different hazard ratios with 95% confidence interval (CI) per comorbidity. These were depicted in a forest plot combined with a P-value for interaction. All hazard ratios were corrected for age, sex, NYHA class and physical limitation score.

A two-sided P-value <0.05 was considered statistically significant.

All analyses were performed using IBM SPSS Statistics version 23 and R: a Language and Environment for Statistical Computing, version 3.0.2. (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Baseline characteristics

A total of 3499 patients were included in our current study. Baseline characteristics are shown in Table 1. We included 2309 patients with HFrEF (66%), 634 with HFmrEF (18%) and 556 patients with HFpEF (16%). Patients with HFpEF were older, more often women, and had higher systolic blood pressures (P < 0.001). Patients with HFrEF were less likely to have a history of hypertension (57%). CKD was present in 50% of patients, anaemia in 36%, obesity and diabetes mellitus in 33%, COPD in 18%, and stroke and thyroid dysfunction in 13% of the patients (Fig. 1). In general, the prevalences of comorbidities were greater in HFpEF, compared with HFmrEF and HFrEF. CKD (56%) and anaemia (46%) had the highest prevalence in HFpEF (respectively P = 0.002 and P < 0.001). COPD was present in 24% of HFpEF patients and 17% in patients with HFrEF (P < 0.001). A history of stroke was found more often in HFmrEF (17%). The prevalence of diabetes differed between HFpEF and HFrEF, where the prevalence within HFmrEF was in between HFpEF and HFrEF, but not significantly different. The prevalences of the other comorbidities are shown in Table 1. The number of comorbidities in patients with HFrEF, HFmrEF and HFpEF differed significantly (P < 0.001). Patients with HFpEF had the highest number of comorbidities, while patients with HFrEF had the lowest number of comorbidities (***Supplementary Fig. 1***). At least 1 comorbidity was found in 84% of the patients with HFrEF, while this was 87% in HFmrEF patients and 94% in patients with HFpEF (P < 0.001). Age-standardized prevalence for the comorbidities is depicted in ***Supplementary Fig. 2***.

3.2. Non-cardiac comorbidities and quality of life

Overall, QoL was lower in HFpEF compared with HFmrEF and HFrEF. When assessing the different domains within the KCCQ, patients with HFpEF had more physical limitations, more symptom frequency and burden, and had the most social limitations (all P < 0.001). Most comorbidities were associated with a significant decline in mean KCCQ score (all P < 0.001), but the decline in mean overall KCCQ score was larger in patients with HFrEF and HFmrEF, compared with patients with HFpEF (Table 2). In patients with HFrEF, each comorbidity, except for thyroid dysfunction, was associated with a significant decline in mean KCCQ score, while in patients with HFpEF COPD (P = 0.002), obesity (P = 0.048) and thyroid dysfunction (P = 0.017) were associated with a decline in QoL. Other comorbidities did not yield a significant difference in mean KCCQ score. ***Supplementary Fig. 3*** shows the difference in overall mean KCCQ score between the subgroups. A difference of ≥5 points was considered to be minimal clinically important. In the total cohort, each of the comorbidities had a minimal clinically important difference, where a decrease of 10 points in mean KCCQ score was seen in patients with COPD. However, in patients with HFrEF, obesity and thyroid dysfunction are no longer associated with a difference in QoL, while the same was true for CKD in HFmrEF. In contrast to the other HF groups, the only comorbidities with a minimal clinical important difference in patients with HFpEF were COPD and thyroid dysfunction. To evaluate the association of comorbidities with QoL in the different HF groups, linear regression was performed (***Supplementary Table 1***). Overall, each non-cardiac comorbidity was associated with a lower KCCQ overall score (all P < 0.001, except for thyroid dysfunction (P = 0.035)). Consistent in each of the HF groups, both COPD and obesity were significantly associated with a lower KCCQ score. However, diabetes was only associated with a lower KCCQ score in HFrEF (P < 0.001), but not in HFmrEF and HFpEF. Both CKD and anaemia were not associated with KCCQ score in HFpEF (respectively P = 0.987 and P = 0.293).

The differences between the groups were less pronounced when using the EQ-5D scale. When assessing the Visual Analog Scale (VAS) score used in the EQ-5D in the total cohort, the presence of each

Table 1
Baseline characteristics.

	HFrEF	HFmrEF	HFpEF	Total	P-value
N	2309	634	556	3499	
Demographics					
Sex (% male)	1744 (75.5)	416 (65.6)	300 (54.0)	2460 (70.3)	<0.001
Age (years)	69 ± 12.2	75 ± 11.1	78 ± 9.8	71 ± 12	<0.001
Systolic blood pressure (mmHg)	123 ± 21	129 ± 22	130 ± 23	125 ± 22	<0.001
Diastolic blood pressure (mmHg)	74 ± 13	72 ± 14	69 ± 14	72 ± 13	<0.001
Heart rate (beats/min)	79 ± 19	75 ± 19	76 ± 18	78 ± 19	<0.001
NT-proBNP (ng/L)	3054 [1158–6930]	1839 [603–4228]	1559 [511–3998]	2390 [842–5672]	<0.001
Non-cardiac comorbidities					
Diabetes mellitus (%)	722 (31.3)	221 (34.9)	198 (35.6)	1141 (32.6)	0.060
Thyroid dysfunction (%)	252 (10.9)	87 (13.7)	97 (17.4)	436 (12.5)	<0.001
Stroke (%)	256 (11.1)	107 (16.9)	91 (16.4)	454 (13.0)	<0.001
COPD (%)	384 (16.6)	103 (16.2)	132 (23.7)	619 (17.7)	<0.001
CKD (%)	1115 (48.3)	334 (52.7)	312 (56.1)	1761 (50.3)	0.002
Anaemia (%)	758 (32.8)	254 (40.1)	253 (45.5)	1265 (36.2)	<0.001
Obesity (%)	679 (29.4)	233 (36.8)	235 (42.3)	1147 (32.8)	<0.001
Peripheral arterial disease (%)	323 (14.0)	127 (20.0)	135 (24.3)	585 (16.7)	<0.001
Number of comorbidities	1.8 ± 1.3	2.1 ± 1.4	2.4 ± 1.3	2.0 ± 1.3	<0.001
Medical history					
Hypertension (%)	1303 (56.5)	443 (70.0)	386 (69.4)	2132 (60.9)	<0.001
Myocardial infarction (%)	998 (43.2)	303 (47.8)	181 (32.6)	1482 (42.4)	<0.001
PCI (%)	471 (20.4)	128 (20.2)	89 (16.0)	688 (19.7)	0.044
CABG (%)	398 (17.2)	129 (20.3)	77 (13.9)	604 (17.3)	0.022
Atrial fibrillation (%)	996 (43.2)	313 (49.5)	275 (49.6)	1584 (45.3)	<0.001
NYHA class					<0.001
I	135 (5.8)	34 (5.4)	16 (2.9)	185 (5.3)	
II	1074 (46.5)	270 (42.7)	194 (34.9)	1538 (44.0)	
III	770 (33.3)	239 (37.8)	235 (42.3)	1244 (35.6)	
IV	130 (5.6)	60 (9.5)	89 (16.0)	279 (8.0)	
Quality of life					
KCCQ					
Physical limitation	54 [29–79]	50 [25–75]	42 [21–67]	50 [29–75]	<0.001
Symptom stability	52 [25–75]	50 [25–75]	50 [25–75]	50 [25–75]	0.008
Symptom frequency	50 [25–70]	45 [25–70]	35 [15–60]	45 [25–70]	<0.001
Symptom burden	42 [27–60]	40 [20–60]	33 [20–53]	40 [20–60]	<0.001
Self-efficacy score	75 [50–88]	75 [50–88]	75 [50–88]	75 [50–88]	<0.001
Quality of life	42 [25–67]	50 [25–67]	42 [25–67]	42 [25–67]	0.134
Social limitation	35 [15–60]	30 [10–55]	25 [5–50]	35 [15–55]	<0.001
Overall score	47 [31–64]	43 [30–59]	38 [24–53]	44 [30–61]	<0.001
EQ-5D					
VAS score	55 [40–70]	59 [48–70]	52 [45–70]	55 [45–70]	0.359

Values are given as means ± standard deviation, median (25th to 75th percentiles) or percentage and frequency.
HFrEF = Heart failure with reduced ejection fraction; HFmrEF = Heart failure with mid-range ejection fraction; HFpEF = Heart failure with preserved ejection fraction; NTpro-BNP = N-terminal pro brain natriuretic peptide; COPD = Chronic obstructive pulmonary disease; CKD = Chronic kidney disease; PCI = Percutaneous coronary intervention; CABG = Coronary artery bypass graft; NYHA = New York Heart Association; KCCQ = Kansas City Cardiomyopathy Questionnaire.

comorbidity significantly lowers the VAS scale, except for obesity ($P = 0.115$). In patients with HFrEF, the presence of COPD ($P < 0.001$), stroke ($P = 0.039$), diabetes ($P < 0.001$), CKD ($P = 0.003$) and anaemia ($P < 0.001$) lowers the VAS score. In HFmrEF patients, only anaemia ($P = 0.003$) is associated with a lower VAS, while in HFpEF only patients with COPD ($P = 0.002$) or thyroid dysfunction ($P = 0.009$) had a significantly lower VAS score.

3.3. Non-cardiac comorbidities and outcome

In the overall cohort, all comorbidities were associated with increased risk for all-cause mortality, except for stroke. Mean follow-up was 25 months. Fig. 2 shows a forest plot with hazard ratios for all-cause mortality and for hospitalisation per HF subgroup. For hospitalisation, the only comorbidity with an increased hazard ratio in HFpEF was thyroid dysfunction, while in HFmrEF CKD, diabetes mellitus, thyroid dysfunction, COPD and anaemia were significantly associated with increased hospitalisation risks. HFrEF showed similar results as in HFmrEF.

Furthermore, in all HF subgroups the presence of CKD was associated with increased risk of mortality (HFpEF Hazard ratio (HR) 1.39, 95% CI 1.03 to 1.87, $P = 0.032$, HFmrEF HR 1.79, 95% CI 1.32 to 2.43, $P < 0.001$ and HFrEF HR 1.49, 95% CI 1.25 to 1.77, $P < 0.001$, respectively). In HFrEF, diabetes mellitus, anaemia and COPD were all associated with significantly higher event rates. In HFmrEF, besides anaemia ($P < 0.001$) no other comorbidities were significantly related with higher mortality rates. In HFpEF, COPD and thyroid dysfunction were both associated with significantly increased event rates. For obesity, a decreased mortality risk was seen in HFpEF (HR 0.60, 95% CI 0.44 to 0.80, $P < 0.001$) and in HFmrEF (HR 0.66, 95% CI 0.48 to 0.89, $P = 0.008$). A significant interaction between comorbidity and LVEF as a continuous variable were seen for diabetes mellitus ($P = 0.031$) and anaemia ($P = 0.043$). Diabetes and anaemia had a stronger association with poor outcomes in HFrEF and HFmrEF, compared with HFpEF.

4. Discussion

We studied 8 non-cardiac comorbidities in a broad cohort of patients with HF. Comorbidities with the greatest prevalence were the presence of CKD, anaemia, diabetes and obesity. For all comorbidities, except for stroke, the prevalence was the highest in patients with HFpEF. We have further shown that most comorbidities were associated with lower QoL, although the difference compared with not having the comorbidity was generally larger in patients with HFrEF compared with

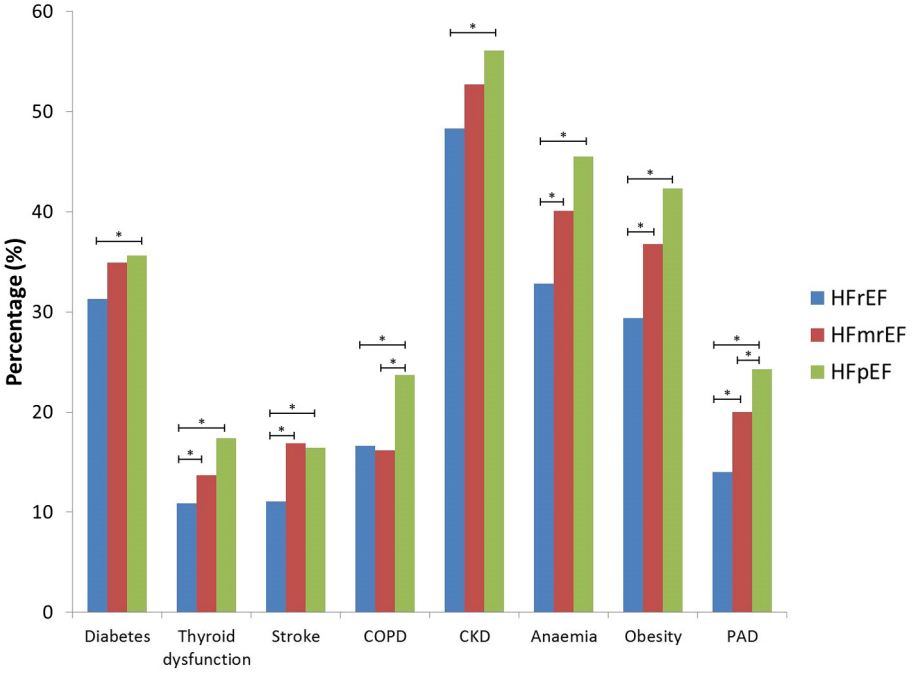

Fig. 1. Prevalence of non-cardiac comorbidities in heart failure groups.

patients with HFmrEF or HFpEF. Furthermore, most comorbidities were associated with an increased risk of mortality, although the presence of diabetes was only associated with higher mortality risks in HFrEF.

4.1. Prevalence of non-cardiac comorbidities

The most common comorbidities in this cohort were CKD and anaemia. These findings are in line with previous studies, where a prevalence of CKD in different cohorts of patients with HF is seen, ranging from 28% up to 55% [1,4,15]. Prevalence of anaemia varies widely in the literature, with numbers ranging from 5 to 60%, in concordance with our study [16,17]. Obesity was present in 33% of our cohort, and its prevalence was particularly high in patients with HFpEF. Obesity is more often seen in patients with HFpEF, and could trouble the diagnosis of HF in these patients [18]. However in our study, patients with HFpEF also had increased levels of NT-proBNP, making misdiagnosis of HF much more unlikely. Diabetes was present in 33% of patients, which is similar to previous studies which report a prevalence ranging from 22% up to 45% [7,19,20]. Novel findings were the prevalences of non-cardiac comorbidities in patients with HFmrEF. To the best of our knowledge, this has not been described before. Prevalences of comorbidities showed a gradual increase from HFrEF to HFmrEF to HFpEF. One of our consistent findings was the fact that comorbidities were more prevalent in patients with HFpEF. Although two previous studies have depicted that non-cardiac comorbidities were more prevalent in patients with HFpEF [6,7], our study additionally focussed on the individual association of each of the comorbidities with QoL and all-cause mortality. To assess whether the higher prevalence of comorbidities in patients with HFpEF was driven by age, we calculated age-standardized prevalences, showing largely similar results. Only for CKD, the similarity in

Table 2
Quality of life in HF subgroups.

	HFrEF		P-value	HFmrEF		P-value	HFpEF		P-value	Total		P-value
Comorbidity present?	No	Yes		No	Yes		No	Yes		No	Yes	
KCCQ overall score												
COPD	50 [32–65]	37 [25–53]	<0.001	45 [31–61]	36 [22–47]	<0.001	41 [27–56]	30 [19–43]	<0.001	46 [31–63]	36 [24–49]	<0.001
Stroke	48 [31–64]	41 [24–60]	<0.001	44 [30–60]	39 [29–51]	0.098	39 [24–54]	34 [23–52]	0.362	45 [30–63]	39 [25–55]	<0.001
Diabetes	50 [33–66]	41 [26–58]	<0.001	45 [31–61]	39 [28–56]	0.039	38 [24–55]	37 [22–51]	0.350	47 [31–64]	40 [26–57]	<0.001
Obesity	48 [32–64]	44 [28–62]	0.011	46 [32–62]	39 [27–56]	0.004	40 [24–56]	36 [24–50]	0.048	46 [31–63]	41 [27–58]	<0.001
Thyroid dysfunction	47 [31–64]	44 [29–60]	0.202	45 [31–60]	34 [24–53]	0.002	39 [24–55]	34 [21–48]	0.017	45 [30–63]	40 [25–56]	<0.001
CKD	51 [33–67]	43 [28–60]	<0.001	46 [31–64]	41 [28–56]	0.010	37 [25–52]	38 [23–54]	0.767	48 [31–65]	42 [28–58]	<0.001
Anaemia	49 [33–66]	42 [27–58]	<0.001	46 [32–64]	39 [28–51]	<0.001	38 [24–56]	37 [24–52]	0.676	47 [31–65]	41 [27–56]	<0.001
PAD	48 [31–64]	42 [27–58]	0.001	45 [31–61]	37 [28–52]	0.016	39 [24–53]	36 [22–52]	0.472	45 [30–63]	40 [26–55]	<0.001
EQ-5D VAS score												
COPD	60 [45–70]	50 [40–65]	<0.001	60 [49–70]	50 [43–65]	0.078	58 [50–70]	50 [40–60]	0.002	60 [45–70]	50 [40–65]	<0.001
Stroke	56 [43–70]	50 [40–70]	0.039	60 [49–70]	50 [40–70]	0.088	55 [45–70]	50 [40–65]	0.191	56 [45–70]	50 [40–70]	0.004
Diabetes	60 [45–70]	50 [40–70]	<0.001	60 [49–70]	55 [45–70]	0.204	52 [40–70]	53 [50–70]	0.839	60 [45–70]	50 [40–70]	0.001
Obesity	55 [43–70]	59 [40–70]	0.737	60 [48–70]	55 [47–70]	0.118	59 [45–70]	50 [40–70]	0.106	55 [45–70]	55 [40–70]	0.115
Thyroid dysfunction	55 [40–70]	55 [40–70]	0.708	60 [49–70]	50 [40–70]	0.220	55 [45–70]	50 [41–60]	0.009	58 [45–70]	50 [40–70]	0.044
CKD	60 [45–70]	52 [40–70]	0.003	59 [49–70]	59 [46–70]	0.492	55 [43–70]	51 [46–69]	0.370	60 [45–70]	52 [40–70]	0.002
Anaemia	60 [45–70]	50 [40–70]	<0.001	60 [50–71]	50 [45–70]	0.003	55 [45–70]	50 [45–68]	0.145	60 [45–70]	50 [40–70]	<0.001
PAD	55 [41–70]	50 [40–70]	0.266	60 [47–70]	50 [48–70]	0.179	55 [45–70]	50 [43–70]	0.748	55 [45–70]	50 [40–70]	0.117

Values are given as median [25th to 75th percentiles]; HFrEF = Heart failure with reduced ejection fraction; HFmrEF = Heart failure with mid-range ejection fraction; HFpEF = Heart failure with preserved ejection fraction; KCCQ = Kansas city cardiomyopathy questionnaire; COPD = Chronic obstructive pulmonary disease; CKD = Chronic kidney disease; PAD = Peripheral arterial disease; EQ-5D = EuroQol five dimensions questionnaire.

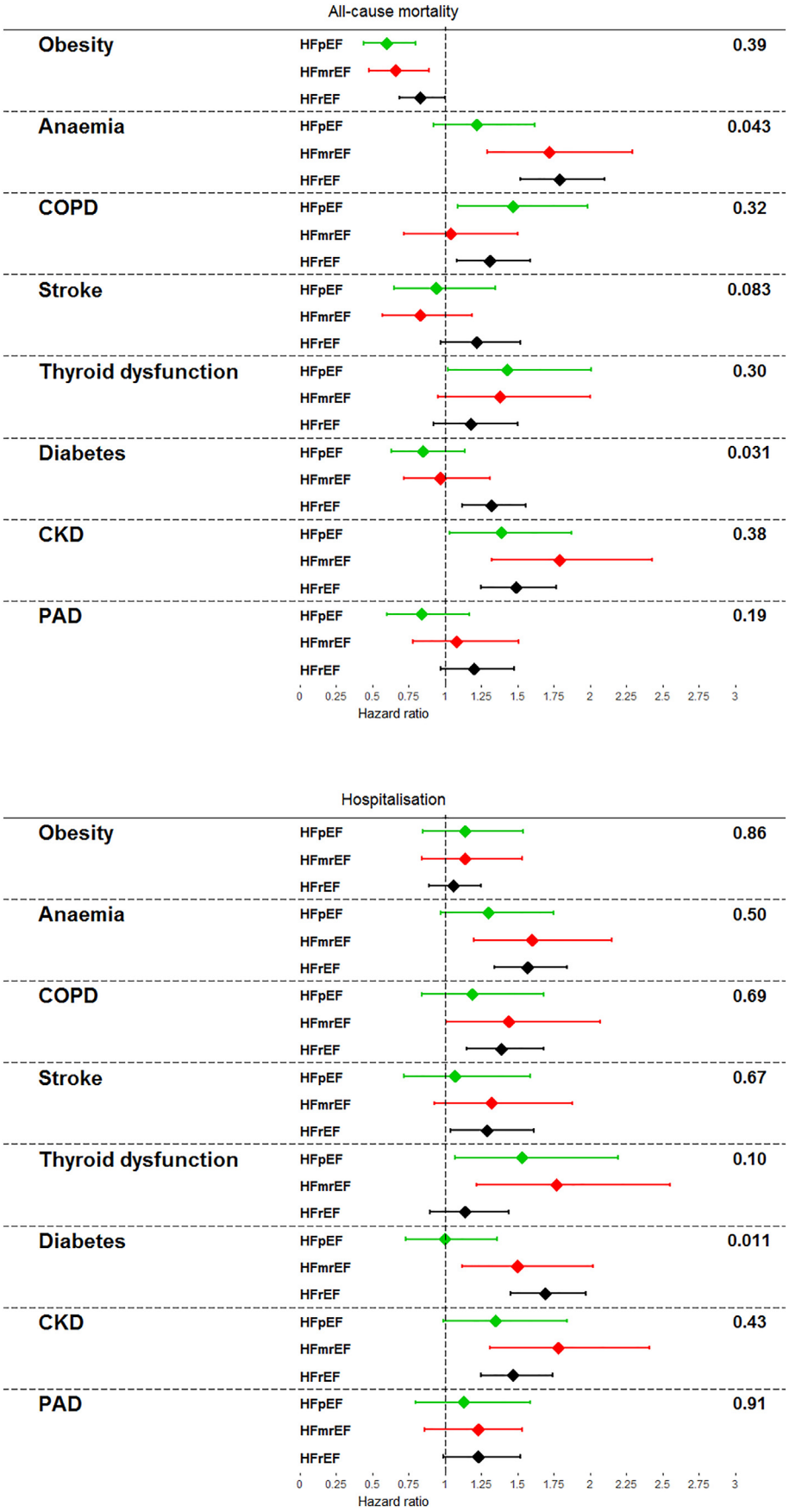

Fig. 2. Forest plot with hazard ratios for all-cause mortality (top) and hospitalisation (bottom) and each comorbidity; corrected for age, sex, NYHA class and physical limitation. On the right is P-value for interaction with heart failure group.

prevalences among HF phenotypes could be argued to be at least partly age driven, as after age adjustment CKD was more frequently observed in patients with HFrEF. For all other comorbidities the prevalence remained greater in patients with HFpEF. Furthermore, multimorbidity was a common finding in our cohort, especially in patients with HFpEF. Braunstein et al. previously showed that nearly 40% of chronic HF patients had 5 or more comorbidities [2]. The prevalence of (multiple) comorbidities increased rapidly during the past two decades [21–23]. In our present study, multiple comorbidities were more often present in patients with HFpEF. This could partly be due to an older age, however, precise mechanisms behind non-cardiac comorbidities and HF are still unclear. However, they do seem an important target for a more holistic approach in the treatment of HFpEF patients [24].

Novel findings in our study also regard the prevalence and associations of comorbidities within HFmrEF. This entity is often referred to as the middle child, which holds true in our cohort for the prevalence of the different comorbidities. The prevalence for each comorbidity was in between HFpEF and HFrEF. A recent review on HFmrEF studies found that HFmrEF might be more similar to HFrEF, especially with regard to the prevalence of IHD [25]. We also found that hazard ratio's for the different comorbidities for HFmrEF showed a more similar pattern to HFrEF compared with HFpEF.

4.2. Influence of comorbidities on quality of life

Comorbidities could influence QoL in several ways [26,27]. The majority of these non-cardiac comorbidities require the use of medication, and polypharmacy is associated with a decrease in functional status of the patient [28]. Furthermore, the majority of these comorbidities are accompanied by a variety of (physical) symptoms, such as fatigue, decrease in general condition and/or shortness of breath. These factors not only limit the patients in functional status, but could also influence their social status and with that an even further decline in QoL. Here, we indeed showed that comorbidities were associated with a lower QoL. In a multivariable analysis, there were more individual comorbidities that were independently associated with overall KCCQ score in HFrEF compared with HFpEF patients. Since comorbidities had a higher prevalence in patients with HFpEF, analyses were repeated within a matched cohort for number of comorbidities with HFrEF. This did not yield any significant difference. A plausible explanation could be that the non-cardiac comorbidities were already present before the onset of HFpEF, while in HFrEF the comorbidities were a consequence of the HF itself. Although this cannot be concluded based on these data, Paulus et al. have previously postulated that comorbidities in HFpEF induce a pro-inflammatory state, resulting in alterations in myocardial structure and functions. Consequently, the comorbidity itself might be the cause -or deteriorating factor- in HFpEF [29]. Our findings might be supportive of this theory.

One of the comorbidities consistently associated with QoL in all 3 HF groups was COPD. HF and COPD often co-exist, with a reported prevalence of approximately 20% within patients with HF. COPD is known to be characterized by a low-grade state of inflammation, and may thus be associated with more frequent cardiovascular events and therefore lowering QoL [30].

4.3. Influence of comorbidities on outcome

We found a consistent and strong association between the presence of non-cardiac comorbidities and outcome. This finding is consistent with previous studies in patients with chronic HF [4,31]. Overall, CKD and anaemia were associated with the highest risks of all-cause mortality. In patients with HFrEF, the presence of diabetes mellitus or COPD was significantly associated with a worse outcome. The presence of COPD may be associated with higher mortality risk in HF, which could partially be due to the fact that patients with COPD are less likely to receive treatment with a beta-blocker and have a reduced exercise capacity [32,33]. However, there are common shared denominators such as inflammation, smoking and/or chronic illness which are known to cause both HF and comorbidities such as COPD [34].

Although in our cohort the association was borderline non-significant, the association between a history of stroke and higher mortality risk was previously shown in a cohort of patients with HFrEF [35]. One reason for this association could be the shared risk factor of atherosclerosis, or the development of thromboembolic events in patients with very low ejection fractions [36].

The precise mechanisms behind the increased mortality risks are still unclear, however, there could be several factors involved in the increased mortality risk observed in patients with (multiple) comorbidities. First of all, HF could result in more comorbidities. Due to fatigue and shortness of breath, patients are more inactive which could play a part in the development of for example diabetes and obesity. Furthermore, patients with multiple comorbidities often represent a more severe HF and are therefore associated with higher mortality risks and higher hospitalisation rates. Lastly, comorbidities may cause worsening HF via medication used to treat these comorbidities, or comorbidities may influence the use of HF medication, influencing their effect on outcome in these patients.

The optimal treatment for both HF and the accompanying comorbidities is a clinical challenge. Especially in HFpEF, HF treatment options are very limited. Therefore optimizing treatment of the separate comorbidities might at least improve the QoL of these patients. This hypothesis will be investigated in a clinical trial, OPTIMIZE-HFPEF, which aims to randomize patients to usual care or intensive treatment of several common comorbidities in HFpEF [37]. It has been depicted in previous research that, especially in HFpEF patients, a more targeted approach might be necessary and therefore treating different phenotypes of HFpEF by not only focussing on the symptoms of HF but also on concurrent comorbidities [38].

4.4. Study limitations

This was a retrospective, post-hoc study, combining two large HF cohorts. In this study in- and exclusion criteria were used, which might result in a more selected population. The majority of patients was recruited in-hospital, which might bias the QoL compared with outpatients included. Another limitation concerns possible underreporting of comorbidities, since they were assessed by the treating physician and/or based on their reported medical history. For COPD, no confirming spirometry was performed which could also result in a false reporting of the comorbidity. Finally, the choice of comorbidities analysed in our study was arbitrary, although this selection allowed us to focus on specific non-cardiac comorbidities. Some comorbidities were not assessed (for example obstructive sleep apnoea syndrome, malignancy, depression and hepatic disease) since data on these comorbidities were not complete.

5. Conclusion

We have studied 8 non-cardiac comorbidities in a broad cohort of patients with HF. The most prevalent non-cardiac comorbidities were CKD, anaemia, diabetes and obesity. The highest prevalence of comorbidities was seen in patients with HFpEF, whereas the prevalence in HFmrEF was consistently in between HFpEF and HFrEF. While in the overall group most of the comorbidities were associated with a lower QoL, this association was more pronounced in patients with HFrEF compared with patients with HFmrEF or HFpEF. Most comorbidities were associated with higher mortality risks, however, the associations with diabetes were only present in patients with HFrEF in contrast to patients with HFmrEF or HFpEF.

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Disclosures

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Appendix A. Supplementary data

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